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Utility of Linked Markers in Genetic Counseling: Estimation of Carrier Risks in X-Linked Ocular Albinism

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We apply a method proposed by Rogatko et al. [1995: Am J Med Genet 59:24–32] to estimate carrier risks using genetic linkage data. The method is illustrated for X-linked ocular albinism. Linkage data from pedigrees were combined with genome mapping data to compute carrier risks for individuals with unknown carrier status based on pedigree data alone. We considered two situations. First, a linkage map with some ambiguity in the gene order was considered. This analysis allows us to examine the effect of incomplete genetic map information on risk computations. Second, published physical and meiotic mapping information was used to derive a linkage map that could be assumed known without ambiguity. In both situations, the mean and median estimate of carrier risk differed significantly from that obtained using pedigree relationships only, in that the computed risk was significantly different from the a priori value of 0.5. The 95% CI's associated with point estimates of risk made using the known map or an map with ambiguity did not overlap in some cases. These results suggest that the risk estimate and the confidence with which a risk estimate can be imparted may depend on the genetic map and marker data used in the risk estimation procedure. We conclude that the method presented here can be used to estimate genetic risk under a variety of analytical conditions. Am. J. Med. Genet. 70: 58–66, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: risk prediction; genetic susceptibility; Bayesian statistics

INTRODUCTION

For genetic diseases in which linkage to a particular chromosomal region has been established, linked marker data can provide better information about disease risk than estimates based on pedigree relationships alone. Traditionally, estimates of the recombination fraction have been used to infer on a probabilistic scale whether an individual with a particular set of linked marker genotypes has inherited the disease (risk) genotype. Risk estimates based on this kind of analytic approach have limited utility because they seldom take into account all information potentially available about the genetic map in the chromosomal region of interest. We have previously proposed methods of risk estimation using linked marker data that take into account linkage information from multiple sources and provide a measure of uncertainty about that risk estimate [Rogatko, 1995; Rogatko et al., 1995].

To illustrate the use of this model in predicting disease risk, we have studied 11 pedigrees with X-linked Nettleship-Falls ocular albinism (OA1). OA1 affects approximately 1 in 150,000 males and produces severely decreased visual acuity, congenital nystagmus, photophobia, variable heterotropia, and misrouting of the optic pathways, resulting in asymmetrical occipital visual evoked potentials and accentuated electroretinographic changes. Female carriers of an OA1 mutation generally do not have clinical manifestations but often show a mosaic pattern of fundal pigmentation thought to represent the effects of random X-inactivation. However, accurate genetic counseling for potential OA1 carriers remains difficult because of variability in clinical manifestations [Schnur et al., 1994]. Deletion mapping and linkage studies have confirmed the presence of a gene for OA1 located on chromosome Xp22.2-p22.3. The recent cloning of this gene [Bassi et al., 1995] makes it possible to develop direct mutation analysis for this defect in some families. However, technical

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limitations often affect the ability to screen for mutations at recently cloned genes [Shattuck-Eidens et al., 1995], and linked markers may continue to be used for some genetic counseling applications. The goal of this paper is to demonstrate the ability to use linked markers in estimating genetic risks in a single family in whom an OA1 mutation has yet to be identified. The specific objectives of the present study are to estimate genetic carrier risks using information about linked markers and to assess the effect of different gene orders and linked markers on the estimation of that carrier risk. We use family linkage data and multipoint genetic maps to estimate risk of carrying a variant (disease) allele at the OA1 locus.

METHODS

Family Data

Our analyses considered data from 119 members of 11 pedigrees that show patterns of disease affection characteristic of X-linked ocular albinism (OA1). Detailed pedigree drawings and clinical evaluation of all 11 pedigrees are presented in Schnur et al. [1991, 1994]. The risk of being a carrier of OA1 was computed for potential carrier women in a single pedigree shown in Figure 1.

The genetic mapping information provided by the 11 OA1 pedigrees was augmented by additional mapping data available from published meiotic mapping studies to help determine gene order. These data included genotypings in families reported by the Centre d'Etude du Polymorphisme Humain (CEPH) Consortium. Marker typings in CEPH pedigrees at each of the loci of interest (see below) were included in the linkage computations.

Molecular Markers

DNA samples on all subjects were obtained from fresh blood or EBV-transformed cells [Schnur et al., 1994]. The molecular markers used in the linkage analysis and carrier risk estimation were *DXS16* (either *MspI* for pSE3.2 L or *BglII* for pXUT23), *DXS85* (*EcoRI* for p782), and *DXS143* (*BcII* for pdic56). A description of these markers can be found in Mandel et al. [1993].

Two analytic situations were considered that made different assumptions about the underlying gene order. First, we computed carrier risks using an ambiguous gene order to examine the effect of having incomplete knowledge about the chromosomal order of markers when computing carrier risk. We used only the available linkage information for the 11 sample families and CEPH data to determine the gene order. Second, we considered the situation where the order of all markers was known based on the available pedigree data as

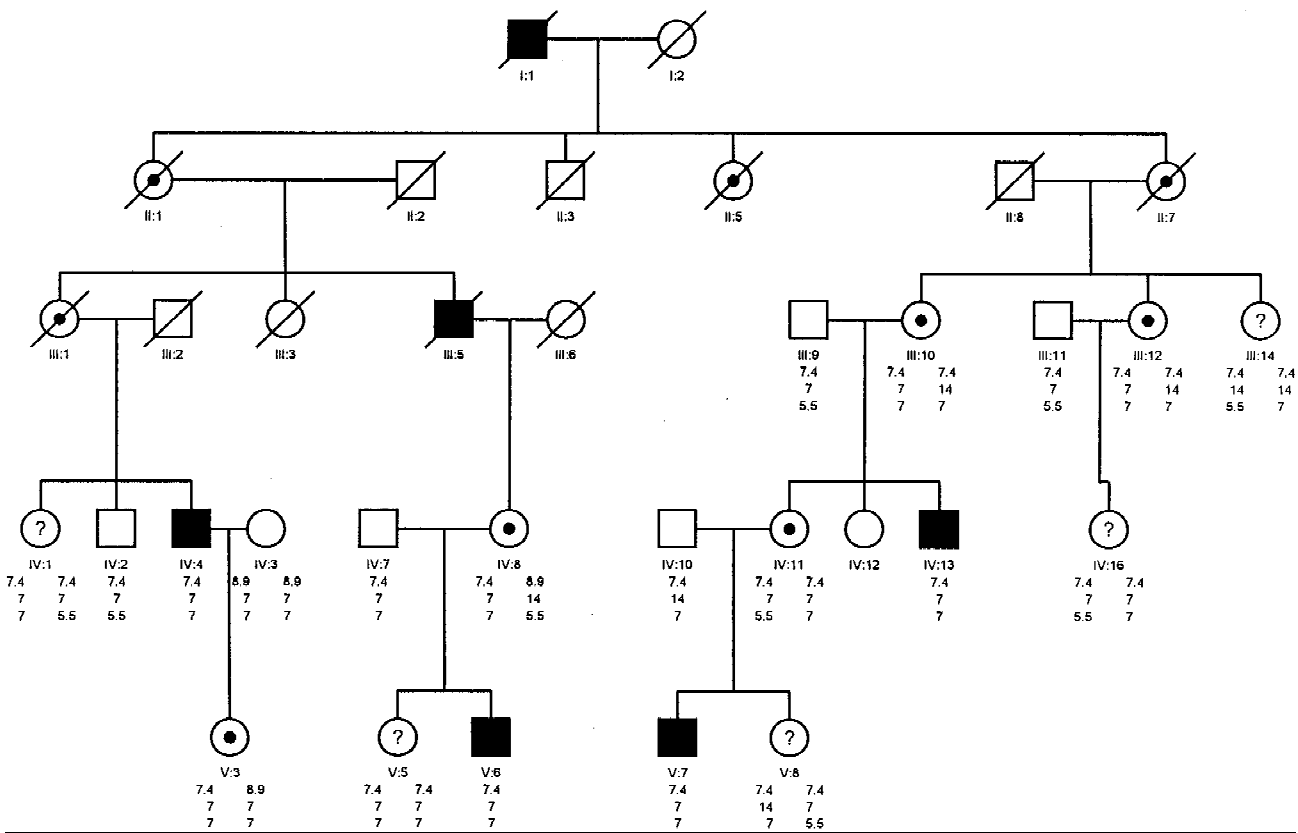

Fig. 1. OA1 pedigree and polymorphism data as described in Schnur et al. [1994] and in the text. Females who are obligate carriers of the mutant OA1 gene are denoted with dots. Females whose carrier status is to be determined here are denoted by a "?." Alleles are denoted by their kilobase molecular weights.

well as previously published meiotic and physical map data. This order has been reported to be *cen-DXS16-DXS85-OA1-DXS143-tel* [Bergen et al., 1990, 1991; Bergen et al., 1993; Charles et al., 1992, 1993; Mandel et al., 1993; Meindl et al., 1993; Schaefer et al., 1993; Schnur et al., 1990, 1991, 1993, 1994]. Because only the closest informative flanking markers are relevant to the carrier risk calculation [Rogatko, 1995], two three-point gene orders consistent with this order were considered: the first gene order was *cen-DXS85-OA1-DXS143-tel;* the second gene order was *cen-DXS16-OA1-DXS143-tel*. This second gene order was considered because the DXS16 locus was more informative than DXS85 in the family studied here.

Analytical Approach

Bayesian methods for risk estimation were used to evaluate carrier risk in selected female pedigree members. Risk computations were carried out using the method described by Rogatko [1995] and Rogatko et al. [1995]. The genetic risk of being a carrier of X-linked ocular albinism is a function of the probability that the individual carries the risk allele. The genetic risk is defined over all gene orders under consideration as $g(r) = (_i \Pr(o_i)\, g(r \mid o_i)$, where $\Pr(o_i)$ is the posterior probability of the i^{th} gene order given the data, and $g(r \mid o_i)$ is the probability density function (pdf) of the risk conditional on the i^{th} gene order and the data. For orders in which the disease locus is flanked by two markers, only the two closest markers need be considered in risk analysis. In the case when the disease locus is adjacent to only one marker, only the closest need be considered. The theoretical basis for these methods is presented in detail by Rogatko [1995].

For the OA1 pedigree data, the functional form of the pedigree likelihood or risk function are extremely difficult to specify. Therefore, an algorithm [Rogatko et al., 1995] was applied that computes g(r) by calculating the likelihood and risk as functions over a range of values of the recombination fraction θ. This algorithm is as follows:

Determine the probability of each gene order. Standard linkage analyses were undertaken to compute $\Pr(o_i)$ using the eleven sample pedigrees and CEPH data [Rogatko and Zacks, 1993]. These analyses were carried out by computing location scores with the statistical software LINKAGE v. 4.9 [Lathrop et al., 1985], although any software package that produces linkage likelihoods could be substituted. The penetrance of OA1 was assumed to be 0.8 in heterozygotes and 0.9 for homozygotes or male hemizygotes. The rare (disease) allele frequency at the OA1 locus was assumed to be 0.00001. The allele frequencies used were those reported in the Genome Data Base (GDB). This first step was omitted when analyses were undertaken assuming a known (unambiguous) gene order.

Compute likelihood and risk values for values of the recombination fraction. The likelihood $l(\theta)$ and risk function $R(\theta)$ for $0 < \theta < 0.5$ were computed when the disease locus of interest flanked all marker loci. Alternatively, the likelihood $l(\theta_1, \theta_2)$ and risk function $R(\theta_1, \theta_2)$ were computed when the disease locus was flanked by two (or more) marker loci. A grid of 1,000 likelihood points along the range of corresponding values of θ or θ_1, θ_2 was computed in this manner using the LINKAGE software. Each risk and likelihood point corresponded to a particular value of θ or θ_1, θ_2. These points formed a bivariate distribution $\{R(\theta); \theta\}$ and $\{l(\theta); \theta\}$ or $\{R(\theta_1, \theta_2); \theta_1, \theta_2\}$ and $\{l(\theta_1, \theta_2); \theta_1, \theta_2\}$. This bivariate distribution was sorted by $l(\theta)$ or $l(\theta_1, \theta_2)$ for computations involving the likelihood, and by $R(\theta)$ or $R(\theta_1, \theta_2)$ for computations involving risk.

Compute a distribution of risk values. The cumulative distribution function (cdf) of carrier risk was calculated by computing the cumulative partial sums of $l(\theta)$ up to $R(\theta)$, or $l(\theta_1, \theta_2)$ up to $R(\theta_1, \theta_2)$. The compound risk cdf was then computed as the average of all risk cdf's weighted by the corresponding posterior probability of each gene order $\Pr(o_i)$. The derivative of this quantity with respect to r was the compound risk pdf of interest. This quantity provided a distribution of risks from which a point estimate of carrier risk and a measure of variability of carrier risk were obtained.

Obtain an estimate of risk and variability about that risk. The risk estimate itself was defined as the mean and median value of the risk distribution (although the mode or other values could be substituted). The measure of variability was obtained as the highest posterior density credible interval (CI) of level α for $R(\theta)$ or $R(\theta_1, \theta_2)$. This interval was defined as any interval [a,b] for $\int_{a<b} g(r)\, dr = \alpha$ such that $g(r_0) \geq g(r_1)$ for any $r_0 \in (a,b)$ and any $r_1 \notin (a,b)$.

All computations were carried out using a DEC workstation with OSF/1 Worksystem Software. The program package COMPRISK [Jordan and Rogatko, 1995] was used in risk estimation and is available for distribution. This program is written in the C language and requires the LINKAGE software package for computation of linkage parameters. This program is available upon request from Mr. Harold Jordan at jordan@canape.fccc.edu.

RESULTS

Gene Order Probabilities

Likelihood calculations were undertaken for both the ambiguous and known gene orders by computing a grid of 1,000 likelihood values. Previous maximum likelihood lod score analyses reported linkage of the markers measured here with the OA1 locus in the sample of families that included the sample pedigree OA-6 [Fig. 1 and Schnur et al., 1994]. There was no evidence for linkage heterogeneity in this sample [Schnur et al., 1994].

For the three linked markers and one disease locus of interest, 12 multilocus gene orders were possible. The probability of each gene order is presented in Table I. Bayesian analysis of gene order using the 11 OA1 pedigrees indicated that the correct gene order was *DXS16-DXS85-OA1-DXS143* with a probability of 0.446,

DXS85-DXS16-OA1-DXS143 with a probability of 0.301, and was *DXS16-OA1-DXS143-DXS85* with a probability of 0.165. All other gene orders were unlikely to be correct, based on a probability of less than 5% using the OA1 pedigrees and CEPH data alone. The inferences obtained from these results are consistent with previous reports of the gene order at this locus: the "correct" order based on all previous meiotic and physical mapping reports is *DXS16-DXS85-OA1-DXS143.* These results indicate that marker data in families had poor ability to distinguish the relative order of *DXS16* and *DXS85.* This was because DXS85 was not very informative in the families studied.

Likelihood and Risk Distributions

Table II presents the computed risks and 95% CI's for individuals III-14, IV-1, IV-16, V-5, and V-8 in the sample pedigree (Fig. 1). The risk distributions used to generate these risk estimates were computed 1) assuming gene order was ambiguous by considering all possible orders of *DXS16, DXS85, OA1,* and *DXS14,* 2) for the "correct" order *DXS16-OA1-DXS143,* and 3) for the "correct" order *DXS85-OA1-DXS143.* As described in the Methods section, 4-point maps need not be considered, because only the closest informative, immediately flanking markers contribute information about carrier risk. The point estimate of risk was 1 for individuals IV-16 and V-5. This result occurred because the women in question inherited the apparently "at-risk" haplotype from their obligate carrier mothers and had a father with a known haplotype. In this situation, risk was completely specified when the daughter has inherited the obligate carrier mother's "at-risk" haplotype.

For one individual (III-14), the 95% CI overlapped the point estimate of risk for each of the gene orders considered. These risks were estimated to be low, suggesting that this individual did not carry the affected haplotype. We present the component likelihood and risk distributions (Figs. 2, 3) for individual III-14 for two reasons: to illustrate the generation of risk estimates and because they represent the situation in which risk estimates can be made in the presence of an apparent recombination event. Two of these likelihood/risk combinations represent the "correct" order of the loci (denoted *DXS16-OA1-DXS143* and *DXS85-OA1-DXS143,* Fig. 3). These two component distributions formed the basis for risk computation when the gene order was known. The likelihood and risk distributions imply that a recombination event has occurred between markers *DXS85* and *DXS143.* This is particularly evident in the two-point risk distributions in Figure 2.

TABLE I. Gene Orders and Their Associated Probabilities

Gene order	Probability that order is correct
OA1-DXS85-DXS143-DXS16	0.0002924
DXS16-OA1-DXS85-DXS143	0.0044721
OA1-DXS85-DXS16-DXS143	0.0000382
DXS16-DXS143-OA1-DXS85	0.0230779
DXS16-DXS85-OA1-DXS143	0.4461347
DXS85-OA1-DXS16-DXS143	0.0001526
OA1-DXS16-DXS85-DXS143	0.0000398
DXS16-OA1-DXS143-DXS85	0.1645900
DXS85-DXS16-OA1-DXS143	0.3011458
OA1-DXS143-DXS85-DXS16	0.0403932
OA1-DXS16-DXS143-DXS85	0.0000454
OA1-DXS143-DXS16-DXS85	0.0196177

The point estimates differed significantly depending on gene order for individuals IV-1 and V-8. In both cases, the point estimate of risk was significantly higher for the order *DXS85-OA1-DXS143* than for order *DXS16-OA1-DXS14.* The risk differences most likely resulted from relatively uninformative marker typings at *DXS85,* which inflated the point estimate toward the baseline (i.e., Mendelian) risk of 0.5. In other words, the use of relatively uninformative marker typings at *DXS85* may have biased the risk estimate toward a risk expected under Mendelian segregation when no marker typings were available. The risk estimate and inestimable 95% CI value for order *DXS85-OA1-DXS143* in individual V-8 (0.1667) suggested that there were insufficient data to estimate the confidence interval about this risk value for this gene order. Note that the limitation in estimation of a 95% CI was inherent to the data, and not a consequence of the model itself. This was a consequence of relatively uninformative marker genotypes at the *DXS85* locus for this individual. Therefore, the point estimate of carrier risk and CI values based on gene order *DXS85-OA1-DXS143* are not useful indices of risk, and would not be appropriate for inclusion in a genetic counseling situation.

The risk estimate for individual IV-1 was low, even though it appears that this individual could have inherited the same haplotype as her affected brother. The reason that the carrier risk in IV-1 is not higher reflects an appropriate ambiguity in the risk distribution due to missing parental genotypes and the common frequency of the alleles comprising the "at-risk" haplotype. For example, marry-in individuals (IV-7, III-9, III-11, and IV-10) also carry haplotypes that are partially or completely identical in state with the "at-risk" haplotype. This generates ambiguity in the risk distribution that is reflected in the relatively low risk estimate for IV-1. Stated differently, one may be easily misled by the apparent sharing of the 7.4-7-7 haplotype between IV-1 and her affected brother (IV-4). In fact, once the commonness of the apparent "at-risk" haplotype and the missing parental information are properly accounted for, a more objective measure of risk in IV-1 can be made. This risk estimate implies that it is not appropriate to consider IV-1 to be at increased carrier risk.

DISCUSSION

We have illustrated a Bayesian approach for using linked markers to estimate carrier risk. We report that risks and CI's can be estimated using linked marker data using either a known or ambiguous gene order. However, the estimates obtained from these analyses varied substantially depending on the markers and gene order that formed the basis of these computations. This appears to be true even in the presence of very

TABLE II. Comparison of Heterozygote (Carrier) Risk Estimates Obtained by Various Methods: Mean Risk Estimate With HPD Credible Interval in [ ]

Pedigree member	Risk using Bayesian method considering 6 (i.e., ambiguous) gene orders	Risk using Bayesian method considering known gene order *DXS16-OA1-DXS143*	Risk using Bayesian method considering known gene order *DXS85-OA1-DXS143*
III-14	0.033 [0.0002, 0.086]	0.038 [0.006, 0.085]	0.025 [0.0004, 0.076]
IV-1	0.178 [0.167, 0.180]	0.172 [0.168, 0.176]	0.209 [0.186, 0.210]
IV-16	1.0000 [a]	1.0000 [a]	1.0000 [a]
V-5	1.0000 [a]	1.0000 [a]	1.0000 [a]
V-8	0.024 [0.0002, 0.053]	0.024 [0.0002, 0.056]	0.1667 [a]

[a]CI was not estimable.

tight linkage, such as in the present example of X-linked ocular albinism. In light of these findings, we discuss 1) the interpretation of risks and CI's as estimated in the present study, and 2) the utility of the proposed method for genetic counseling.

Interpretation of Risk and CI Values

We present a Bayesian approach to risk assessment that illustrates how genetic information, including the genetic map, can be used in a genetic counseling situation. Three points can be made about the results of the present analysis. First, the closest (fully) informative marker is crucial in risk computation, even though it is physically further from the disease gene of interest than a second, less informative marker. Second, the proposed method can provide a more objective measure of risk than might be obtained by other methods. We have demonstrated an individual (IV-1), who appears

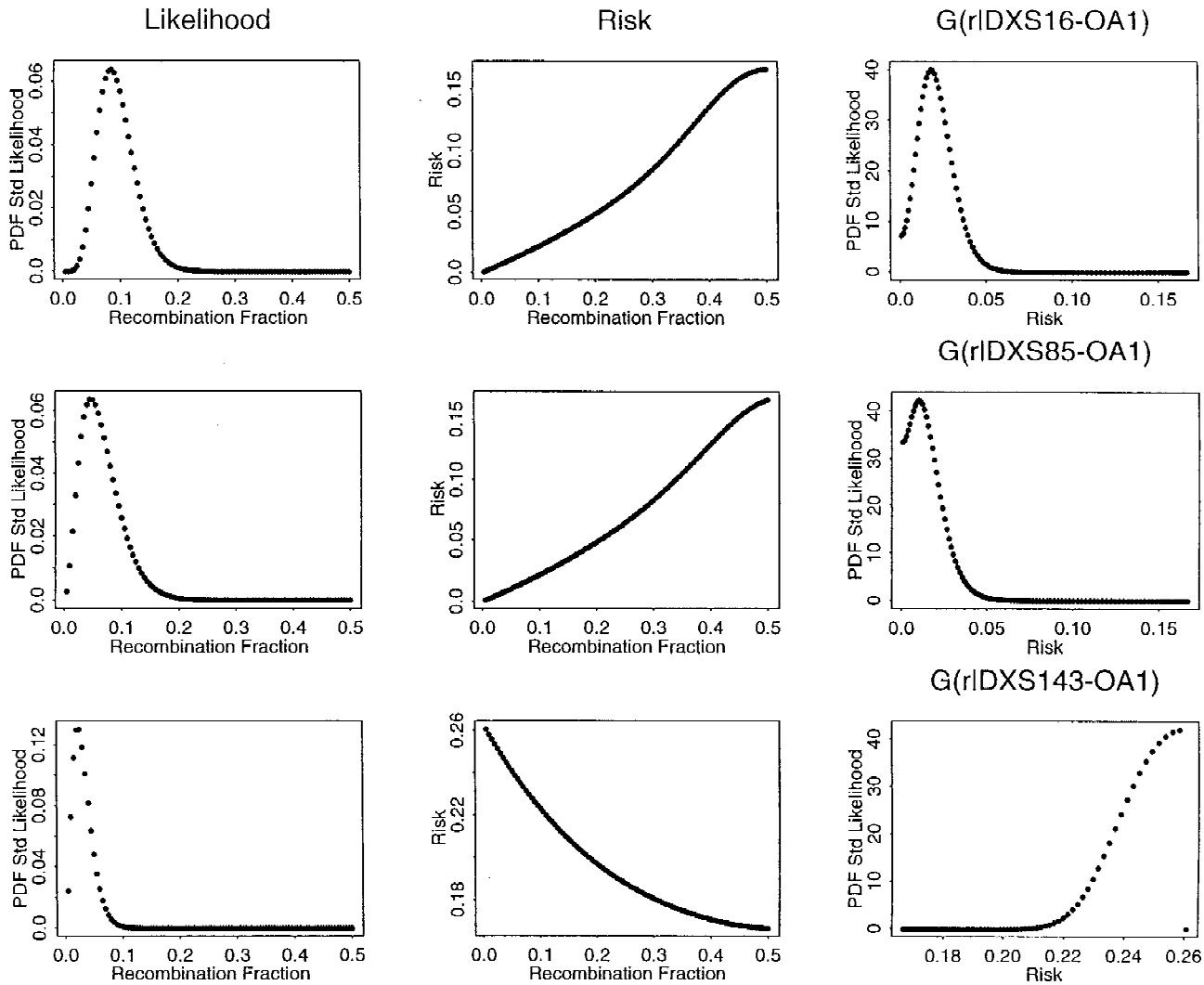

Fig. 2. Likelihood, Risk, and G(r | o) component distributions for individual III-14: Disease locus flanking all marker loci.

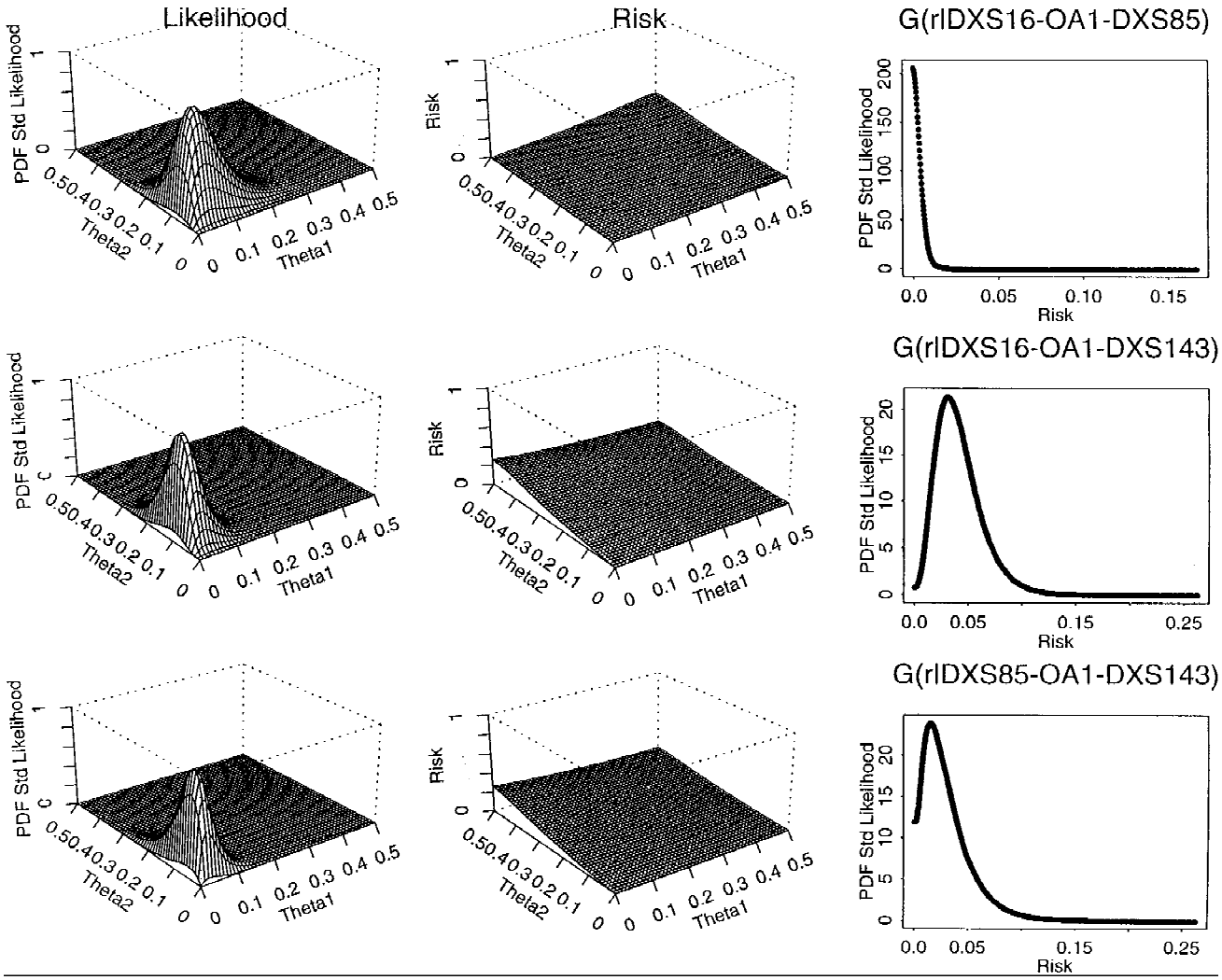

Fig. 3. Likelihood, Risk, and G(r | o) component distributions for individual III-14: Two marker loci flanking disease locus.

to be at increased risk because she shares the sample haplotype with her affected brother (IV-4), may in fact not be at elevated carrier risk once other pedigree data are accounted for. In this case, the apparent "at-risk" haplotype in question is shared by both affected and obligate carriers in the family as well as unaffected marry-ins, who are presumably identical in state but not identical by descent. Because this woman's parental genotypes are also unknown, the risk computations imply that it is not appropriate to infer that this women is at elevated carrier risk. Third, we observed that risk estimates for potential carriers of a mutant OA-1 gene may depend on knowledge about gene order. In the present examples, these differences were quite small in the absolute sense, and it is unclear whether these small magnitude differences in the CI's would lead a medical geneticist to interpret or impart a risk estimate differently depending on the gene order used for the risk computation. However, the present results suggest that improved knowledge about gene order or haplotype ambiguity can have a large impact on the ability to accurately estimate risk of carrying a disease gene.

The ability to obtain meaningful estimates of disease risk is a crucial step in the genetic counseling process. Unfortunately, little research has been conducted to date that would guide the genetic counselor in applying or interpreting the information contained in a statistical estimate of risk and its associated distribution or CI. While most medical geneticists and some patients may understand the estimation of unknown probabilities, many will not be readily able to interpret risk estimates and the associated uncertainty that accompanies them. There has been considerable debate about the value of uncertainty measures about risk estimates. The full distribution of a risk estimate may add little to a patient's understanding of their risk. The added concept of "confidence" about the risk estimate may therefore cloud the ability to communicate risk information. In particular, a complicated risk distribution may be difficult to interpret.

Conversely, additional information about the complete distribution of risk can help to enlighten the patient about their risk and its interpretation. The shape of the risk distribution can provide a sense of the qual-

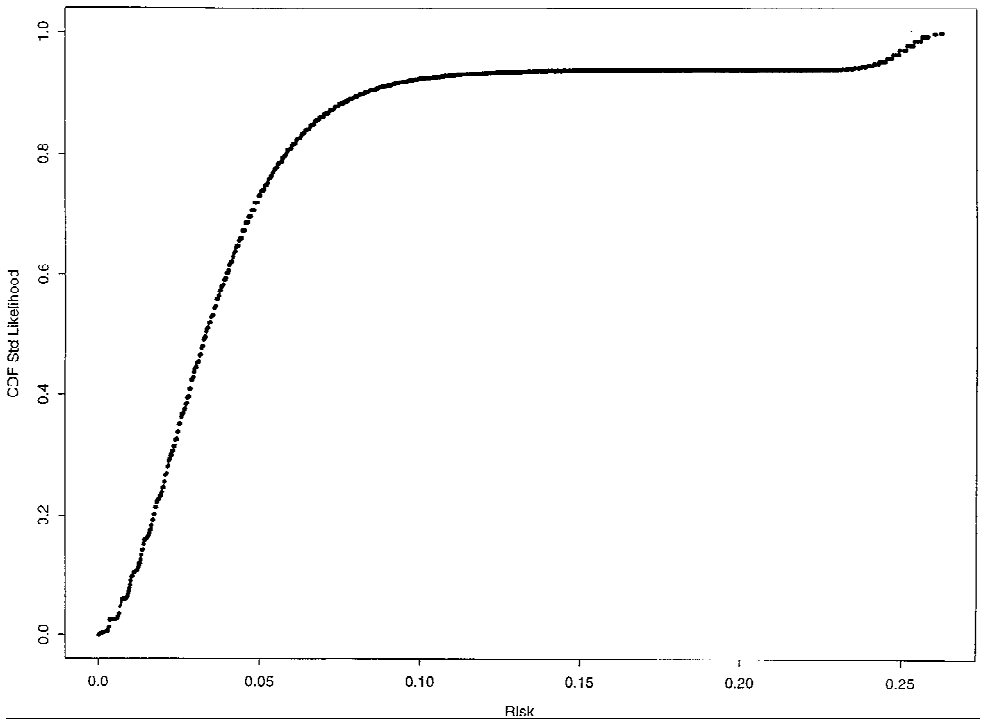

Fig. 4. Cumulative density function (cdf) of risk for individual III-14 considering all gene orders.

ity of the risk estimate [Rogatko et al., 1995]. For example, a plot showing a sharp peak that coincides with the risk estimate may provide visual reinforcement about the certainty with which that estimate was made. In contrast, a rather flat risk distribution may help convince the patient that the provided risk estimate has been made with less confidence.

A compromise approach advocates that the full distribution of the risk function and associated CI's can be best interpreted by the counselor, who then can interpret the risk distribution information in a qualitative way to the patient. For example, when the counselor computes a point estimate of risk that has a very wide CI or an unusually shaped distribution (e.g., bimodal), the counselor may be able to communicate the degree of confidence they have in the risk estimate. This interpretation is limited by the ability of the counselor to understand and convey information about variability in a risk estimate, but it is likely to be more reliable than the patient's interpretation of the same information.

Finally, we have presented the mean values to summarize the risk distribution. Other measures of central tendency, such as the median or mode, may also be appropriate. Under certain distributional conditions, these values may coincide, and the choice of estimator will be less important to the counseling process. However, when the distribution of risk has an unusual shape (e.g., bimodal), the chosen estimate may not adequately represent the complete distribution. This can be dealt with in part by visually examining the entire distribution, and then choosing an appropriate estimator [Box and Tiao, 1992].

Utility of the Proposed Method in Risk Estimation

Numerous approaches to the estimation of risk have been proposed. These range from estimates obtained from Mendelian rules of segregation to more complex Bayesian statistical approaches such as that proposed here. While each of these risk estimation methods has a valid place in the medical geneticist's repertoire, we propose that a more comprehensive method of estimating risk may be preferable to simpler methods of risk estimation.

First, a more comprehensive method of risk estimation accounts for all of the information available that may contribute to risk. There is no collapsing or summation of data during the estimation procedure, so that the ultimate risk distribution is a more accurate reflection of the original data. This is particularly important when the risk estimate is derived from a large amount of data such as multiple linked markers measured in complex pedigrees. Second, the method presented here provides a measure of uncertainty (or precision) about the estimate of risk that is based on an objectively determined distribution. As described in the previous section, this quantity can provide valuable information to the counselor, and potentially to the patient as well. Third, the method proposed here is not limited to models that impose linear or other potentially unrealistic constraints. While a prior (e.g., uniform) risk distribution must be specified, the choice of this prior distribution is flexible, and the results of risk computation using a variety of prior distributions can be compared. Models can be written that more accurately reflect the relationship between multiple risk factors and disease.

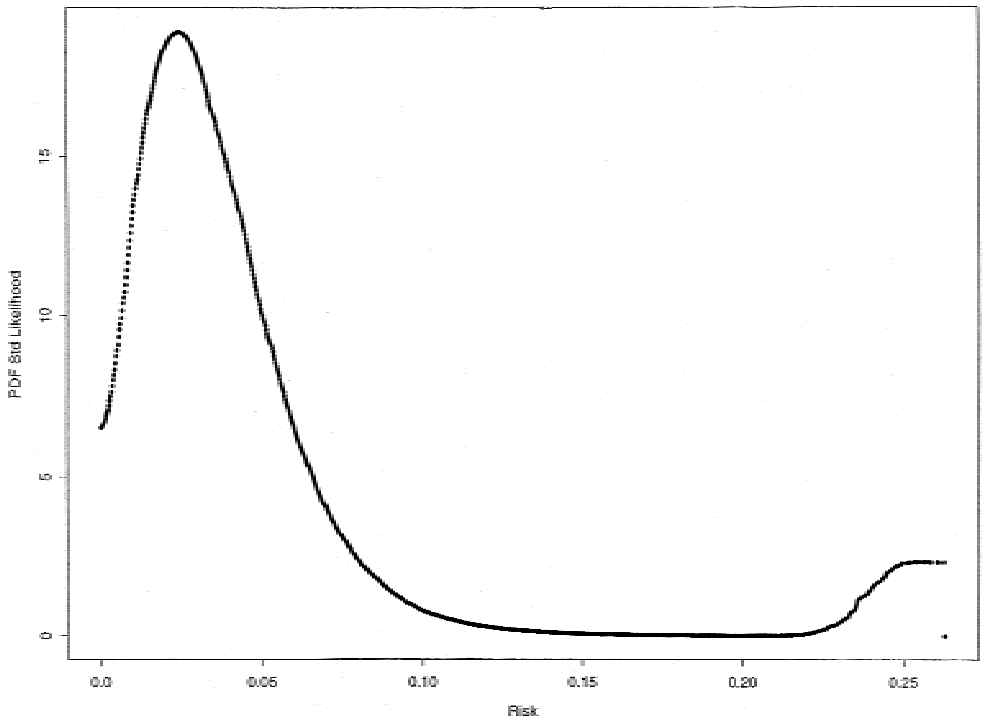

Fig. 5. Probability density function (pdf) of the risk for individual III-14 considering all gene orders.

Therefore, a more comprehensive risk estimation method, such as that proposed here, can incorporate other data relevant to an individual's risk. These data include epidemiologic risk factors, demographic characteristics, and mutations in known genes. The ability to simultaneously account for many genotypes or other risk factors may make the proposed approach suitable for risk estimation in diseases with a complex etiology such as cancer, diabetes, or hypertension.

The information about risk obtained from the proposed method is in some ways more complete, more accurate, and more useful than more simplistic risk estimates. However, it has yet to be determined whether the cost of computing a more complex estimate rather than a more simple estimate provides additional benefit to the patient. Furthermore, the impact of these different risk estimates (with or without CI's) on the patient's subsequent behavior is unclear. There is little information in the published literature on which to base the impact of these differences in risk estimates, nor is there adequate information to assess the degree to which knowledge about different risks will impact health behaviors. Substantial additional research is required by medical geneticists, clinical psychologists, and other health professionals to determine the benefit of this and other measures of risk to the patient.

Summary

The growing body of knowledge about genetic and environmental risk factors for many diseases demands that flexible models of risk estimation be developed. The risk estimate should incorporate as much information as is relevant and available. This includes adjusting risk for specific exogenous exposures, endogenous genes or physiology, and demographic characteristics. While not considered in the present analysis, the model used here can incorporate all of these classes of information. This includes statistical models that can address interactions among risk factors. We are currently examining additional models within the context of the statistical structure presented here that can be applied by medical geneticists in traditional prenatal and pediatric situations as well as risk computation for cancer, coronary artery disease, and other chronic illnesses.

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